To: Members and Guests of the Antiviral Products Advisory Committee

From: The Division of Antiviral Products

Re: October 19-20, 2006, Advisory Committee Meeting to discuss clinical trial design issues in the development of products to treat chronic hepatitis C

Date: September 18, 2006

Introduction

The purpose of this document is to provide background information for the October 19th and 20th advisory committee meeting, which is being convened to discuss issues on clinical trial design for the development of therapeutic products to treat chronic hepatitis C infection. Currently, five interferon alpha biologic products given either as monotherapy or in combination with oral ribavirin drug products are approved for the treatment of chronic hepatitis C (CHC). Many believe pegylated interferon alpha (PEG-Intron®, Pegasys®) given in combination with oral ribavirin represents current optimal therapy with successful outcomes achieved in 50-80% of treatment-naïve CHC patients depending on virus genotype. Despite the advances made in the treatment of this serious viral infection, additional progress in development of HCV therapeutics is needed. The current standard-of-care for management of CHC is associated with considerable toxicity and cost. Further, its success has been limited in certain treatment-naïve subgroups and has been especially disappointing in treatment-experienced patient populations. In response, sponsors of approved therapies are exploring innovative approaches to improve efficacy. In addition, several small molecule anti-hepatitis C drugs targeting the HCV polymerase, protease and other HCV targets are in various phases of development. Given recent advances in the field, the Division believes this is an opportune time to discuss clinical trial design issues for hepatitis C product development.

The attached references and information/analyses included in this document are intended to aid the committee as they address these issues. Initially, in planning for this advisory committee meeting, the Division asked sponsors of INDs for the treatment of HCV to submit written opinions on clinical trial design issues. These opinions were sought through a series of questions which were similar but not identical to those draft questions you have before you. Sponsors who provided written opinions are referred to as IND holders in this backgrounder. The IND holders were asked to support any conclusions with references or data from their own drug development. This background document incorporates information from these submissions.

The advisory committee will be asked to address a number of discussion points/questions. In brief, the discussion points focus on the following issues: the

appropriate and essential patient groups to study in CHC drug development, selection of control arms for Phase 3 studies, the most appropriate endpoint or combination of endpoints to evaluate efficacy, and the type of information to collect during longer-term follow-up in Phase 3 studies. Background information pertinent to each of these issues is presented in the following sections along with the corresponding questions/discussion points (in boxes at the beginning of each section below) the committee is asked to address.

We would like the committee to focus on both demographics (race/ethnicity) and disease characteristics when considering patient groups that are most appropriate for establishing safety and efficacy in principal Phase 3 studies that are part of a marketing application.

After discussing the important subgroups that should be studied and included in a marketing application, the Division would like the committee to comment on the types and numbers of studies and the number of patients needed to obtain data in various subgroups. The committee should comment on whether it is advisable or necessary to conduct separate studies for certain disease characteristics or whether larger studies should be conducted that stratify randomization based on baseline characteristics.

Discussion Points

1.0 Patient Populations

Advisory Committee Discussion Points

1a. Which patient populations are strongly recommended for inclusion at the time of initial approval? In particular, comment on:

- stage of disease (compensated and decompensated cirrhosis)
- treatment experience (naïve and interferon+ ribavirin experienced)
- genotype (1 and 4 or 2 and/or 3 or some other grouping)
- co-morbidities (HIV and/or HBV co-infection)
- pre and post liver transplantation
- pediatrics
- racial and ethnic groups

Hepatitis C therapeutic products are needed globally. While an estimated 3.2 million individuals in the United States are chronically infected with HCV (HCV antibody positive for at least 6 months), approximately 170 million persons are

chronically infected worldwide. Therefore, a worldwide development program is likely. However, from a regulatory standpoint, a marketing application needs to contain safety and efficacy data that includes a fair representation of the U.S. CHC epidemic population.

The U.S. epidemic is evolving. In the U.S. the incidence of new infections has declined from an average of 240,000 per year in the 1980s to about 26,000 per year in 2004. The risk factors for acquisition have changed with sizable reductions in infections attributable to blood transfusion. Injection drug use is currently most important. At the same time, the chronically infected population is aging. Data collected in 1988-1994 indicated peak prevalence in the 30-39 year olds; in 1999-2002, the peak prevalence was in the 40-49 year old group. Models based on known prevalent cases, and the increased risk of cirrhosis and hepatocellular carcinoma with longer duration of infection, predict the rate of liver-related complications will increase in the next 10-20 years. Absence of early clinical symptoms, normal liver enzymes and failure of HCV transmission risk screening may suggest an increase in the number of patients with both compensated and decompensated cirrhosis presenting for treatment. Of note, interferon based treatment is currently contraindicated for patients with decompensated liver disease and where studied, has demonstrated lower response rates in those with compensated cirrhosis compared to patients with lesser amounts of liver fibrosis.

There are six HCV genotypes, and each is differentially amenable to antiviral therapy. Genotype 1 remains the most prevalent genotype in the U.S. with prevalence as high as 90% among important subgroups such as African Americans. Although not more pathogenic, genotype 1 has demonstrated significantly lower response rates to interferon-based therapy and is, therefore, the focus of new treatment development. Genotypes 2 and 3 appear to have a better response to interferon-based treatment than genotype 1. Some data suggests that genotype 2 and 3 infections are associated with differences in clinical presentation and perhaps should be studied separately. Data also suggest that genotype 3 patients with high viral loads are slower to respond to treatment and therefore require longer treatment than genotype 2 or other genotype 3 patients with low viral loads. Genotype 4 is not prevalent in the U.S., has an intermediate sensitivity to interferon-based therapy and is generally treated like genotype 1.

Treatment-naïve adult subjects with relatively early stage histologic changes (mild-to-moderate fibrosis), high baseline viral load and genotype 1 infection represent the majority of patients with CHC in the U.S. and Europe. Some of the IND holders have indicated that this population, by virtue of size and homogeneity, is particularly suited to the initial demonstration of safety and anti-viral efficacy of broadly active new anti-HCV agents. Notably, the treatment-experienced population is the most rapidly growing CHC patient population with few treatment options. This latter group is increasingly populated by patients

infected with genotype 1 who fail to achieve a sustained virologic response (SVR) with pegylated interferon/ribavirin therapy. Patients in this group have more advanced histology and present a more urgent need for effective treatment.

The U.S. CHC population co-infected with HIV and/or HBV continues to grow owing to shared transmission risk factors. It is appreciated that co-infection with HIV is associated with more rapid HCV liver disease progression. In the era of Highly Active Antiretroviral Therapy (HAART), severe HCV-induced liver disease has proven to be a more serious cause of morbidity in the HCV/HIV co-infected population than in those with HIV alone. Additionally, response rates to pegylated interferon/ribavirin regimens are reduced in the HCV/HIV co-infected patient compared to the HCV monoinfected population, and the opportunities for drug interactions between HCV and HIV therapies raise both safety and efficacy concerns.

Co-infection with HBV poses somewhat different challenges since interferon-based therapy may be beneficial and ribavirin is not anticipated to adversely affect HBV response. The general response from the IND holders is that studying the CHC population co-infected with HIV and/or HBV should not be part of an initial HCV (monoinfection) treatment registration program.

End-stage liver disease caused by hepatitis C is currently the leading indication for liver transplantation. Post-transplant recurrence of HCV infection is nearly universal and a major cause of liver transplant failure. Pre-transplant viral load is correlated with the severity of recurrent liver disease and strategies to reduce viral load during the immediate pre-transplant period should be considered. Given that these patients are extremely fragile and have decompensated liver disease, safety and tolerability issues are crucial, especially with interferon-based regimens. Prevention of HCV recurrence, similar to what was achieved with Hepatitis B Immunoglobulin (HBIG) and small molecule antivirals after liver transplantation for HBV is an important focus of study. Interferons as immune stimulators are contraindicated in the immediate post-transplant period, so direct targeting of HCV replication is preferred. In the post-transplantation setting, genotype 1 appears more aggressive than genotypes 2 and 3 in development of liver failure. The consensus from IND holders is to delay study of this patient group until further data is acquired from other patient populations.

There are a relatively smaller number of pediatric HCV patients. The majority of pediatric HCV patients acquire their infection through mother-to-child transmission. The differences in disease manifestations in pediatric HCV patients compared to adult patients generally includes milder disease, less frequent extra-hepatic manifestations, and fewer co-morbid conditions associated with liver progression. Given these differences, some have argued against aggressive treatment. Nonetheless, advanced fibrosis or cirrhosis does occur and treatment is needed. Some IND holders suggested pediatric “post approval” clinical studies

and pediatric access programs during Phase 2-3 development for promising new agents for patients with severe HCV morbidity.

As previously noted, African Americans have higher rates of infection with the more difficult to treat genotype 1 than other racial/ethnic groups. When results of interferon-based treatment of subjects with genotype 1 are examined, African Americans had lower sustained viral response rates than non African Americans when both were treated with similar doses and durations of interferon and ribavirin as reported by Bräu, N. et al. In contrast, sustained viral response rates for genotypes 2 and 3 were similar across racial groups. We do not know if these differences pertain only to interferon-based regimens. Most IND holders regarded inclusion of African American and Hispanic individuals into registrational trials (Phase 3) of new agents as desirable but suggested that investigator trials or Phase 4 postmarketing trials could be means of actually conducting studies of possible racial/ethnic differences due to previously encountered difficulties in enrollment. During your deliberations, please include discussion regarding overcoming barriers to enrollment of different racial and ethnic groups, particularly those with historically low levels of study participation.

Advisory Committee Discussion Points

1b. For the purposes of pursuing an indication for novel agents in treatment experienced non responder patients please comment on the following components as inclusion criteria in clinical development studies

- Previously treated with 1 or more IFN-containing regimens that include PEG-IFN and RBV; and
- Failure to achieve a ≥ 2 log reduction in HCV RNA at Week 12, or HCV detectability at Week 24 or beyond while on therapy (confirmed by a repeat test); and
- Compliance documented over the first 12 weeks of previous therapy to confirm receipt of at least 80% of the prescribed RBV and PEG-IFN dose.

The term “non-responders” to prior interferon-based therapy when used loosely refers to a heterogeneous population. When describing a study population for inclusion in clinical trials or in product labeling, greater precision is necessary. The “non-responder” population can actually be divided into the following subgroups:

- patients with no significant response (the true non-responder)

- patients with partial response which the AASLD defines as having achieved ≥ 2 log reduction in HCV RNA at Week 12 but who failed to achieve HCV undetectability at Week 24 or beyond while on therapy

- relapsers who are defined as those who achieve undetectable status during therapy but cannot maintain this response during the follow-up period

- and lastly, relapsers who initially achieve undetectable status but relapse during therapy

The mechanisms underlying these disparate responses are not understood and it is possible, once issues of treatment adherence are eliminated, that each response identifies a different subpopulation that may also respond differently to non-interferon products. For accurate interpretation of clinical trial data of novel agents in the interferon non-responder patient population , there must be agreement on a definition of what constitutes prior therapy including definitions of adequate treatment adherence.

Advisory Committee Discussion Points

1c. Please discuss whether or not it is appropriate in a clinical trial of prior interferon treatment non-responders to study true responders, partial responders and relapsers together and why.

Re-treatment with interferon in a standard-of-care comparator arm would likely be more successful with the relapsers and less successful with the true non-responders. Over or under-representation by the different subgroups could impact apparent comparator efficacy and confound interpretation of trial data. In addition, as discussed above, the underlying reasons for disparate responses among these three subgroups to similar interferon/ribavirin exposures are unknown. It is possible that the disparate responses that define heterogeneity among these subgroups are confined to interferon-alfa/ribavirin treatment alone. In such a case, these patients may respond to novel agents in a more homogeneous manner. Alternatively, these responses may identify subpopulations with differing unappreciated attributes which may impact upon responses to novel agents. A conservative approach might include refining the population as much as possible to achieve the greatest homogeneity and interpretability of data. While this may improve interpretability, if too narrow it may be inadequate to support product approval.

2.0. Selection of Controls

Advisory Committee Discussion Points

Are placebo controls or delay of initiation of therapy acceptable, and, if so, of what duration? In your answer, please consider the following patient populations:

- treatment-naïve versus treatment-experienced
- compensated and decompensated liver disease.

There is consensus among IND holders that for treatment-naïve compensated liver disease CHC patients, the most appropriate control regimen is parenteral pegylated interferon alpha and oral ribavirin for either 24 or 48 weeks depending on genotype. Interferon placebos are essentially impossible owing to interferon's well recognized toxicity, ineffectiveness of ribavirin monotherapy, the impracticality of parenteral placebos, and the absence of spontaneous untreated SVR. Novel product placebos added to standard-of-care for comparison to three drug study regimens or for short durations 2-4 weeks as monotherapy comparison with active product were acceptable for all populations.

Some IND holders did indicate instances where placebo or deferred administration could be acceptable for the treatment-naïve compensated patient. This patient group has a low likelihood of rapid progression and includes patients with minimal fibrosis and those with normal or essentially normal ALTs. Therefore, a short duration of placebo or delay in instituting treatment might be acceptable if later cross-over to an active treatment was assured. Additionally, placebo controls might be appropriate for early safety trials. The suggested acceptable duration of therapy delay for treatment-naïve compensated patients were variable ranging from 4 to 12 weeks.

Among treatment-experienced compensated liver disease patients participating in studies with a SVR primary endpoint, IND holders indicated placebo controls or delay in treatment (up to 24 months) might be acceptable for non-responders to pegylated interferon/ribavirin. For those studies in which HCV eradication is unachievable and other endpoints such as normalization of transaminases are used, a placebo of a study drug might be acceptable. Few of the IND holders commented on patients with decompensated liver disease. Of those that did, there was little support for use of placebo controls or treatment delays but one IND holder stated that with sufficient safety mechanisms in place, placebo controlled or treatment delay might be possible for non-interferon agents in patients with decompensated liver disease.

3.0 Study Design

3a, b, and c Evaluation of Efficacy: Endpoints Compensated Liver Disease

Advisory Committee Discussion Points

Considering the patient populations identified in question number 1 and the necessity that endpoints for registration be clinically meaningful, please answer the following:

a. Which primary endpoint(s) should be used in clinical trials? Please discuss histologic, viral and biochemical endpoints.

b. When should the assessment of the primary endpoint be made? Please comment on the pros and cons of an SVR 12 (12 weeks after cessation of treatment) versus SVR 24 (24 weeks after cessation of treatment).

c. If a study has treatment arms of a different duration, when should assessment of SVR 24 be made? Specifically, should it be made 24 weeks after end of treatment for all arms, or 24 weeks after the end of treatment based on the arm with the longest duration of therapy?

Compensated liver disease would encompass all CHC patients up to and including compensated cirrhosis. Compensated cirrhosis is defined by the absence of clinical complications of liver disease (ascites, variceal hemorrhage and encephalopathy) and presence of preserved hepatic synthetic function (albumin $\geq$ 3.5 g/dL, total bilirubin $\leq$ 1.5 mg/dL and prothrombin time international normalized ratio (INR) $\leq$ 1.5).

For the treatment-naïve compensated liver disease CHC patient, there is consensus by IND holders that the Sustained Virologic Response (SVR) should be used as the primary efficacy endpoint. The predictive value of SVR for viral eradication was recently corroborated by researchers from France who performed Transcription Mediated Amplification (TMA) testing of patients achieving SVR after treatment of CHC. Of the 217 patients tested up to 17 years after achieving SVR, only 5 had detectable HCV RNA, 1 in PBMCs and 4 in liver tissue. The timing of the SVR is a bit more controversial. The majority of IND holders concurred with the current guidelines of 24 weeks (SVR 24) after the end of treatment. A few IND holders argued that since 98% of relapses occur within 12 weeks of the end of treatment, an SVR 12 may be appropriate with an investigational treatment that fulfills an unmet medical need or is demonstrated to be significantly better than the standard-of-care, if corroborated by the SVR 24. Importantly, SVR is only validated for interferon-based treatments. Some IND holders stated the Agency should insist upon demonstration of durability of SVR

for new molecular entities as demonstrated by negative HCV RNA and ALT levels for at least 1-3 years following completed treatment.

For the treatment-experienced population, recommended primary efficacy endpoints were more varied. Non-responders to standard unpegylated interferon/ribavirin, pegylated interferon monotherapy or responder relapsers have a reasonable expectation of attaining an SVR with retreatment with pegylated interferon/ribavirin. For these patients, the consensus among IND holders was to use SVR 24. Non-responders (true non-responders, partial responders) to an adequate course (at least 80% treatment compliant) of pegylated interferon/ribavirin standard-of-care have little presumption of attaining an SVR with retreatment (approximately 5-10% by IND holders estimates). There was divergence among the IND holders as to what primary efficacy endpoint to select for this patient population. Most continued to favor SVR with attainment of an Early Virologic Response at 12 weeks (EVR 12) defined as $\geq$ 2 Log_{10} decrease in HCV RNA at 12 weeks of treatment as a definitive futility endpoint. In support of the use of the EVR 12, the negative predictive value (NPV) of an EVR 12 with interferon-based therapy was shown to be 97% for treatment-naïve patients and 100% for non-responders (null response). Some IND holders recommended attainment of the EVR 12 itself as a primary efficacy endpoint coupled with postmarketing commitments to validate this surrogate.

Other primary endpoints were suggested for those in the non-responder patient population whose lack of response or intolerance to pegylated interferon/ribavirin makes viral suppression rather than viral eradication the ultimate goal of treatment. Some suggested histologic and biochemical primary endpoints for this group. Others suggested that for this patient population, the HIV model might be applicable with efficacy interpreted as levels of viral suppression. No IND holder offered actual levels of viral load suppression that might be clinically meaningful.

The other early virologic marker, the Rapid Virologic Response (RVR 4) defined as an undetectable HCV viral load (<50 IU/mL) at 4 weeks of therapy was mentioned by a few IND holders as potentially valuable as a co-primary endpoint for both treatment naïve and non-responders. Ferenci, Peter et al. in 2005 published a Positive Predictive Value (PPV) of 75% achieving SVR for treatment naive patients achieving an RVR 4 on interferon based therapy. The use of RVR 4 might be especially suited to the HIV model discussed above where viral suppression is the primary endpoint. RVR 4 might be valuable in studying different treatment durations. In 2006, Jensen, Donald M. et al. observed that 24% of genotype 1 patients achieved an RVR 4 which had a PPV of 89% for SVR after 24 weeks of pegylated interferon/ribavirin.

For both treatment-naïve and non-responders except as noted above, histologic and biochemical endpoints were considered most appropriate as secondary endpoints because of their lack of specificity and sensitivity. Histologic endpoints

in particular were noted to have a 20% sampling error. Further, one IND holder suggested that only the most motivated/compliant patients may consent to a second liver biopsy which might skew the findings toward positive. A situation in which histologic and biochemical end points would be useful as primary endpoints for CHC patients with compensated liver disease were agents not expected to eradicate the virus such as peginterferon for non-responders, statins etc.

There was consensus among the IND holders that the SVR should be measured at a number of weeks from the end of treatment rather than at the same timepoint for different treatment durations. The FDA recommends that everyone should receive a follow-up evaluation at the same time rather than 24-weeks post-treatment in order to ensure that treatment effects are not confounded by evaluation time. For example, if 24 weeks of treatment is compared to 48 weeks of treatment in patients with genotypes 2 or 3 the primary analysis of the SVR should occur at Week 72. Otherwise, patients in the 24 week treatment arm will be evaluated at Week 48 while patient in the 48-week treatment arm will be evaluated at Week 72. In your deliberations, please address this issue and provide the Agency with your recommendations regarding the optimal time for SVR endpoint measurement.

3 d. Study Design Options

Advisory Committee Discussion Points

Please discuss the following study designs

- adding the investigational agent to standard-of-care (SOC)
- use of a dose of PEG-IFN lower than SOC or lower than SOC and of shorter duration + investigational agent
- ribavirin substitution
- use of two or more investigational agents
- monotherapy

<u>Adding the investigational agent to standard-of-care (SOC)</u>
The majority of IND holder responses suggested adding a third agent to pegylated interferon/ribavirin is the preferred clinical design for treatment-naïve patients especially the difficult to treat genotype 1 patients. It might be useful in the treatment-experienced population to be guided by RVR 4 or EVR 12. Such an agent, if oral, could be compared to its placebo. A parenteral novel product might present a greater challenge. Depending on the efficacy and safety characteristics of the novel agent, triple therapy maintained throughout a treatment course, administered for a defined period followed by a period of consolidation with standard-of-care or administered for a defined period (12-24 weeks) followed by off treatment follow-up was suggested.

Use of a dose of PEG-IFN lower than SOC or lower than SOC and of shorter duration + investigational agent

Of the IND holders who addressed this issue, there appeared to be consensus that while decreased dosage and/or duration of pegylated interferon therapy with acceptable or improved efficacy might be possible with co-administration of novel agents, it would be important that pivotal studies include SOC comparator arms with and without the novel agent.

Ribavirin substitution

The mechanism of action by which oral ribavirin improves SVR rates for interferon alfa treatment of chronic hepatitis C is not currently understood. Therefore, many IND holders were reluctant to study a novel agent in substitution for ribavirin until the agent had demonstrated activity in addition to standard-of-care including ribavirin. In the presence of such data, a direct acting antiviral agent such as a polymerase or protease could be compared in combination with pegylated interferon versus the standard-of-care. Demonstration of non-inferiority for the pegylated interferon/novel agent in terms of efficacy and comparable or better safety/tolerability is needed for approval action. To test the additive or synergistic effects of the new agent, its administration as a monotherapy for up to 12 weeks prior to adding the pegylated interferon was suggested.

Use of two or more investigational agents

Novel investigational regimens with two or more anti-HCV products with complementary mechanisms of action such as polymerase inhibitor(s) and/or protease inhibitor(s) are considered important new directions for the recalcitrant CHC populations, including standard-of-care non-responders. The known viral kinetics of HCV resembles those of HIV. Therefore, it is anticipated that multiple drug therapy will be needed for successful treatment, but demonstration of the contribution of each component of the regimens to the overall treatment effect is important. Initial discussions are underway to investigate novel multi-drug regimens for the well characterized pegylated interferon/ribavirin non-responder populations. Multi-drug regimens could be compared in this same population versus retreatment with standard-of-care or deferred treatment with novel regimen to establish placebo-like control period. IND holders suggested a concurrent pegylated interferon/RBV treatment period perhaps with EVR 12 assessment should be incorporated to confirm non-responder status. In addition to the standard-of-care non-responder population, other potential study populations might include patients for whom interferon/ribavirin is contraindicated such as patients with decompensated liver disease or severe anemia.

As a prelude to inclusion in combination studies, both FDA and IND holders agree that a novel agent would have to demonstrate anti-HCV activity (as determined by HCV RNA reductions) over a specified period. These specified

periods would likely be of short duration (up to 14 days) but depending upon the agent's mechanism of action, longer periods of monotherapy might be appropriate if viral resistance development concerns are satisfied. Drug-drug interaction studies should be considered prior to combination studies, especially if the metabolism profile of the individual drugs suggested interaction potential. Ideally, drugs to be studied would have different mechanisms of action and differing resistance patterns. To minimize safety concerns, the use Rapid Virologic Response (RVR4) at 4 weeks to guide these novel agent clinical trials is possible.

Monotherapy

Sponsors supported limited monotherapy treatment periods in clinical trials. Their main concern was that the high daily turnover of HCV RNA and low fidelity of the HCV NS5b polymerase would increase the chances of development of antiviral resistance with longer duration monotherapy. No support was given for anything other than short duration of interferon monotherapy except in special populations such as those with ESRD.

3 e. Evaluation of Efficacy: Endpoints Decompensated Liver Disease

Advisory Committee Discussion Points
What degree of change is clinically meaningful for patients with decompensated liver disease when using change in CPT or MELD score as an endpoint?

Few IND holders responded to this question. The discussion that follows represents responses received enhanced by data from the current medical literature.

Without liver transplantation, the 5-year survival of CHC patients with decompensated liver disease is 50%. The goals of antiviral therapy in this group are different from those among the compensated liver disease group and include: slowing the progression of the clinical disease, improving hepatic function, reversing the complications of liver disease and reducing the need for liver transplantation. Secondary goals are eradication of HCV RNA (SVR) to prevent recurrence of HCV viremia after transplantation and reduction in HCV RNA to reduce severity of post-transplantation liver disease. A major concern regarding treatment of decompensated liver disease patients is the safety of interferon and ribavirin administration. This patient group is at increased risk of treatment related bone marrow suppression and life-threatening decline of hepatic function. The published literature regarding use of these products in this group is limited. In one study of patients prior to transplantation as reported by Everson, Gregory T., on-treatment, virological responses in 39% and SVR in 22% have been achieved. Those patients achieving SVR pre-transplant remained virus-free post-

transplantation. After transplantation, even higher virologic responses are possible. In July 2006, Neumann, Ulf et al. reported a 68% viral response during treatment and SVR of 36% using pegylated interferon/ribavirin. This therapy was, according to the authors “associated with a number of severe side effects”. However with treatment of these side effects no patients were withdrawn from the study. Histologic change from baseline to 72 weeks after beginning treatment was one of the secondary endpoints measured in this study. It was observed that the yearly fibrosis progression rate using the Scheuer-Desmet criteria was significantly lower during interferon treatment than in the same patients prior to treatment. In addition, the mean inflammation scores were also statistically decreased in this same comparison. Results from other studies have not been as favorable.

Two scoring systems are available to gauge hepatic function and prioritize deceased donor (DD) liver transplant allocation. The Child Turcotte Pugh (CTP) scoring system has been in use for 30 years and consists of 3 categories A, B, and C with category A representing compensated cirrhosis, and C the cirrhotic group with the greatest transplantation need. Since 2002, the CTP scoring system was superseded by the Model for Endstage Liver Disease (MELD) scoring system to stratify patients for prioritization for orthotopic liver transplantation. Whereas the CTP system uses 5 empirically selected parameters including 2 subjective clinical factors to create its three categories, the MELD system uses three statistically selected objective factors (serum creatinine, serum total bilirubin and INR) creating a continuous numeric score.

Both scoring systems attempt to quantify residual liver function which correlates with liver disease complications and the urgency of transplantation. Mortality from liver disease in both scoring systems does correlate with increasing scores but neither is considered truly linear. CTP is more familiar by virtue of its long-term usage. The MELD system is preferred by many transplantation centers because this system is scientifically/statistically derived and provides a continuous score rather than categorical. On the other hand, the discriminant values of various MELD score are not as well established as those apparently provided by the CTP categories.

Efficacy endpoints of non-interferon/ribavirin based HCV treatments capable of possibly improving hepatic function and/or eradicating or suppressing HCV RNA in the decompensated population may make use of CTP and/or MELD as efficacy endpoints in addition to HCV RNA levels. Chan, Henry L-Y et al. recently published an evaluation of MELD and CTP as predictors of mortality in decompensated chronic hepatitis B. In his report from Hong Kong, Chan determined that both systems were able to predict mortality at 3 and 12 months in this hepatitis B population in which only 3% underwent liver transplantation. In this study, patients with MELD scores under 20 could not be differentiated. Those with MELD scores of 21-30 and >30 had distinctly different and higher mortality rates. This work suggests that reducing MELD scores from higher values to

below 20 may have clinical importance. For CTP, considerable difference between observed mortality among the three categories (A, B, C) was observed. Further, it is noted that reduction of CTP from group C to group B is interpreted as clinical improvement and removes patients from the transplant list in some transplant centers. In your discussion, please address the use of these scoring systems as clinical improvement surrogates.

One IND holder suggested that since the goal of treatment in the decompensated liver disease population is a significant level of virologic suppression leading to subsequent improvement in liver histology, a composite endpoint: serum HCV RNA reduction of > 1 $\log_{10}$ IU/mL with a histologic response (2 point in Knodell HAI and no worsening in fibrosis) would be clinically meaningful.

4.0 Long Term Follow-up

Advisory Committee Discussion Points
Beyond the assessment of the primary endpoint for registration, what is the appropriate duration of follow-up for chronic hepatitis C infection, and what kind of information should be gathered? Please discuss duration of follow-up for different patient populations (especially pediatrics), and, in particular, when an investigational agent is not added to standard-of-care.

The majority of IND holders expressed confidence in the durability of the SVR endpoint achieved with interferon-based treatment. For patients achieving SVR with interferon-based treatments, many of the IND holders felt no further follow-up was required. One did express interest in the use of registries to assess development of known sequelae of CHC such as portal hypertension or hepatocellular carcinoma. For patients achieving SVR using novel agents, some suggested 1-3 years follow up of HCV RNA and perhaps also ALT since the durability of the SVR in these instances is not known. Some IND holders conservatively suggested 5-10 year follow-up of all patients achieving SVR. For cirrhotics, transplant recipients, HIV/HCV coinfected, and immunodeficient patients who achieve SVR, more frequent follow-up of HCV RNA was suggested. No data was offered in support of this recommendation.

For patients who fail to achieve SVR, semi-annual follow-up to monitor the state of liver function was recommended.

For situations where viral eradication as documented by SVR may not be achievable and histologic and biochemical endpoints are used; 4-5 year follow-up was recommended.

A majority of IND holders agree that resistance testing should be performed weekly depending on the drug target and resistance mutations identified.

Bibliography

Alter H. “Viral Hepatitis.” Hepatology. 43(2) (2006): S230-S234.

Blackard JT, Kemmer N, Sherman KE. et al. “Extrahepatic Replication of HCV: Insights Into Clinical Manifestations and Biological Consequences.” Hepatology. 44(1) (2006): 15-22

Botta, F et al. “MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study” Gut (2003) 52 134-139

Bräu, N. et al. “Black patients with chronic hepatitis C have a lower sustained viral response rate than non-Blacks with genotype 1, but the same with genotypes 2/3, and this is not explained by more frequent dose reductions of interferon and ribavirin.” Journal of Viral Hepatitis. 13 (2006): 242-249.

Brown, Robert S. et al. “Model for End-Stage Liver Disease and Child-Turcotte-Pugh Score as Predictors of Pretransplantation Disease Severity, Post transplantation Outcome, and Resource Utilization in United Network for Organ Sharing Status 2A Patients” Liver Transplantation 8 No 3 (2002) 278-284

Chan, Henry L-Y et al. “Evaluation of Model for End-Stage Liver Disease for Prediction of Mortality in Decompensated Chronic Hepatitis B” American Journal of Gastroenterology 101 (2006) 1516-1523

Chen, Stephen L. and Timothy R. Morgan. “The Natural History of Hepatitis C Virus (HCV) Infection.” International Journal of Medical Sciences. 3(2) (2006): 47-52.

De Francesco, Raffaele and Giovanni Migliaccio. “Challenges and successes in developing new therapies for hepatitis C.” Nature. 436 (2005): 953-960.

Durand, Francois et al. “Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD” Journal of Hepatology 42 (2005) S100-S107

Everson, Gregory T. “Should we treat patients with chronic hepatitis C on the waiting list?” Journal of Hepatology 42 (2005) 4, 456-461

Everson, Gregory T. “Management of cirrhosis due to chronic hepatitis C” Journal of Hepatology 42 (2005) S65-74

European Paediatric Hepatitis C Virus Network. “A Significant Sex – but Not Elective Cesarean Section – Effect on Mother-to-Child Transmission of Hepatitis C Virus Infection.” Journal of Infectious Diseases. 192(11) (2005): 1872-1879.

Feld, Jordan J. and T. Jake Liang. “Hepatitis C – Identifying Patients with Progressive Liver Injury.” Hepatology. 43(2) (2006): S194-S206.

Ferenci, Peter et al. “Predicting sustained virologic responses in chronic hepatitis C patients treated with peginterferon alfa-2a(40kd)/ribavirin” Journal of Hepatology, 43 (2005) 425-433

Gelderblom, Huub C. et al. “Clinical performance of the new Roche COBAS TaqMan HCV Test and High Pure System for extraction, detection, and quantitation of HCV RNA in plasma and serum.” Antiviral Therapy. 11(1) (2006): 95-103.

Iorio, Raffaele et al. “Chronic Hepatitis C in Childhood: An 18-year Experience.” Clinical Infectious Diseases. 41 (2005): 1431-1437.

Jensen, Donald M. et al. “Early Identification of HCV Genotype 1 Patients Responding to 24 Weeks Peginterferon α-2a (40kd)/Ribavirin Therapy” Hepatology, 43, (2006) 954-960

Kontorinis, Nickolas et al. “Treatment of hepatitis C virus in HIV patients: a review.” AIDS. 19(3) (2005): S166-173.

Kuo, A. and N.A. Terrault. “Management of Hepatitis C in Liver Transplant Recipients.” American Journal of Transplantation. 6 (2006): 449-458.

Mast, Eric E. et al. “Risk Factors for Perinatal Transmission of Hepatitis C Virus (HCV) and the Natural History of HCV Infection Acquired in Infancy.” The Journal of Infectious Diseases. 192 (2005): 1880-1889.

Marcellin, Patrick et al. “Long-Term Histologic Improvement and Loss of Detectable Intrahepatic HCV RNA in Patients with Chronic Hepatitis C and Sustained Response to Interferon-α Therapy” Annals of Internal Medicine 127 (1997) 875-881

Neumann, Ulf et al. “Treatment of Patients with Recurrent Hepatitis C after Liver Transplantation with Peginterferon Alfa-2B Plus Ribavirin” Transplantation 82(1) July 2006, 43-47

Nguyen, Mindie H. and Emmit B. Keeffe. “Prevalence and Treatment of Hepatitis C Virus Genotypes 4, 5, and 6.” Clinical Gastroenterology and Hepatology. 3 (2005): S97-S101.

Núñez, Marina and Vincent Soriano. "Current concepts in the management and treatment of hepatitis C in HIV-infected patients." Annals of Hepatology. 4(3) (2005): 151-160.

Said, Adnan et al. "Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease" Journal of Hepatology 40 (2004) 897-903

Schooley, Robert T. "HIV and Hepatitis C Virus Coinfection: Bad Bedfellows." International AIDS Society. 13(4) (2005): 112-116.

Sherman, Morris et al. "Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy." Gut. (2006).

Shire, Norah J. and Kenneth E. Sherman. "Clinical Trials of Treatment for Hepatitis C Virus Infection in HIV-Infected Patients: Past, Present, and Future." Clinical Infectious Diseases. 41(1) (2005): S63-S68.

Strader, Doris B. "Understudied Populations with Hepatitis C" Hepatology 36 (2002) S226-S236

Strader, Doris B et al. "Diagnosis, Management and Treatment of Hepatitis C" Hepatology 39 (2004):1147-1171

Sugawara, Yashuiko and Masatoshi Makuuchi. "Living Donor Liver Transplantation for Patients With Hepatitis C Virus Cirrhosis: Tokyo Experience." Clinical Gastroenterology and Hepatology. 3 (2005): S122-S124.

Sulkowski, Mark S. "Treatment algorithm for the management of hepatitis C in HIV-coinfected persons." Journal of Hepatology. 44 (2006): S49-S55.

Sy, Theodore and M. Mazen Jamal. "Epidemiology of Hepatitis C Virus (HCV) Infection." International Journal of Medical Sciences. 3(2) (2006): 41-46.

Wiesner, Russell et al. " Model for End-Stage Liver Disease (MELD) and Allocation of Donor Livers" Gastroenterology 124 (2003) 91-96

Wong, Winnie and Norah Terrault. "Update on Chronic Hepatitis C." Clinical Gastroenterology and Hepatology. 3 (2005): 507-520.

Wright, Teresa L. "Treatment of Patients with Hepatitis C and Cirrhosis" Hepatology 36 (2002) S185-194

Yu, ML et al. "A randomized trial of 24- vs. 48-week courses of PEG interferon α-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan." Liver International. 26 (2006): 73-81.